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Hodgkin-Huxley Models

The core mathematical framework for modern biophysically based neural modeling was developed half a century ago by Sir Alan Hodgkin and Sir Andrew Huxley. They carried out an elegant series of electrophysiological experiments on the squid giant axon in the late 1940s and early 1950s. The squid giant axon is notable for its extraordinarily large diameter (~0.5 mm). Most axons in the squid nervous system and in other nervous systems are typically at least 100 times thinner. The large size of the squid giant axon is a specialization for rapid conduction of action potentials that trigger the contraction of the squid's mantle when escaping from a predator. In addition to being beneficial for the squid, the large diameter of the giant axon was beneficial for Hodgkin and Huxley because it permitted manipulations that were not technically feasible in smaller axons that had been used in biophysical studies up to that point. In a well-designed series of experiments, Hodgkin and Huxley systematically demonstrated how the macroscopic ionic currents in the squid giant axon could be understood in terms of changes in Na^+ and K^+ conductances in the axon membrane. Based on a series of voltage-clamp experiments, they developed a detailed mathematical model of the voltage-dependent and time-dependent properties of the Na^+ and K^+ conductances. The empirical work lead to the development of a coupled set of differential equations describing the ionic basis of the action potential (Hodgkin and Huxley, 1952), which became known as the Hodgkin-Huxley (HH) model. The real predictive power of the model became evident when Hodgkin and Huxley demonstrated that numerical integration of these differential equations (using a hand-cranked mechanical calculator!) could accurately reproduce all the key biophysical properties of the action potential. For this outstanding achievement, Hodgkin and Huxley were awarded the 1963 Nobel Prize in Physiology and Medicine (shared with Sir John Eccles for his work on the biophysical basis of synaptic transmission).

Electrical equivalent circuits

In biophysically based neural modeling, the electrical properties of a neuron are represented in terms of an electrical equivalent circuit. Capacitors are used to model the charge storage capacity of the cell membrane, resistors are used to model the various types of ion channels embedded in membrane, and batteries are used to represent the electrochemical potentials established by differing intra- and extracellular ion concentrations. In their seminal paper on the biophysical basis of the action potential, Hodgkin and Huxley (1952) modeled a segment of squid giant axon using an equivalent circuit similar to that shown in Fig. 1. In the equivalent circuit, the current across the membrane has two major components, one associated with the membrane capacitance and one associated with the flow of ions through resistive membrane channels. The capacitive current I_c is defined by the rate of change of charge q at the membrane surface: $I_c = dq/dt$. The charge $q(t)$ is related to the instantaneous membrane voltage $V_m(t)$ and membrane capacitance C_m by the relationship $q = C_m V_m$. Thus the capacitive current can be rewritten as $I_c = C_m \, dV_m/dt$. In the Hodgkin-Huxley model of the squid axon, the ionic current I_{ion} is subdivided into three distinct components, a sodium current I_{Na}, a potassium

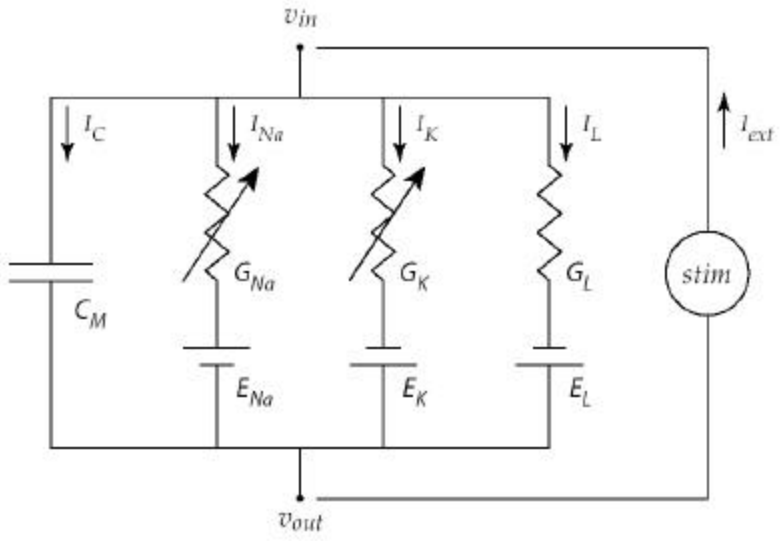

Fig. 1 Electrical equivalent circuit for a short segment of squid giant axon. The capacitor represents the capacitance of the cell membrane; the two variable resistors represent voltage-dependent Na^+ and K^+ conductances, the fixed resistor represents a voltage-independent leakage conductance and the three batteries represent reversal potentials for the corresponding conductances. The pathway labeled "*stim*" represents an externally applied current, such as might be introduced via an intracellular electrode. The sign conventions for the various currents are indicated by the directions of the corresponding arrows. Note that the arrow for the external stimulus current I_{ext} is directed from outside to inside (i.e., inward stimulus current is positive), whereas arrows for the ionic currents I_{Na}, I_K and I_L are directed from inside to outside (i.e., outward ionic currents are positive). After Hodgkin & Huxley (1952).

current I_K, and a small leakage current I_L that is primarily carried by chloride ions. The behavior of an electrical circuit of the type shown in Fig. 1 can be described by a differential equation of the general form:

$$C_m \frac{dV_m}{dt} + I_{ion} = I_{ext} \qquad (1)$$

where I_{ext} is an externally applied current, such as might be introduced through an intracellular electrode. Equation 1 is the fundamental equation relating the change in membrane potential to the currents flowing across the membrane.

Macroscopic Ionic Currents

The individual ionic currents I_{Na}, I_K and I_L shown in Fig. 1 represent the macroscopic currents flowing through a large population of individual ion channels. In HH-style models, the macroscopic current is assumed to be related to the membrane voltage through an Ohm's law relationship of the form $V=IR$. In many cases it is more convenient to express this relationship in terms of conductance rather than resistance, in which case Ohm's law becomes $I = GV$, where the conductance G is the inverse of resistance, $G = 1/R$. In applying this relationship to ion channels, the equilibrium potential E_k for each ion type also needs to be taken into account. This is the potential at which the net ionic current flowing across the membrane would be zero. The equilibrium potentials are represented by the batteries in Fig. 1. The current is proportional to the

conductance times the difference between the membrane potential V_m and the equilibrium potential E_k. The total ionic current I_{ion} is the algebraic sum of the individual contributions from all participating channel types found in the cell membrane:

$$I_{ion} = \sum_k I_k = \sum_k G_k (V_m - E_k) \quad (2)$$

which expands to the following expression for the Hodgkin-Huxley model of the squid axon:

$$I_{ion} = G_{Na}(V_m - E_{Na}) + G_K (V_m - E_K) + G_L (V_m - E_L) \quad (3)$$

Note that individual ionic currents can be positive or negative depending on whether or not the membrane voltage is above or below the equilibrium potential. This raises the question of sign conventions. Is a positive ionic current flowing into or out of the cell? The most commonly used sign convention in neural modeling is that ionic current flowing *out* of the cell is positive and ionic current flowing into the cell is negative (see subsection on Sign Conventions for more details).

In general, the conductances are not constant values, but can depend on other factors like the membrane voltage or the intracellular calcium concentration. In order to explain their experimental data, Hodgkin and Huxley postulated that G_{Na} and G_K were voltage-dependent quantities, whereas the leakage current G_L was taken to be constant. Thus the resistor symbols in Fig. 1 are shown as variable resistors for G_{Na} and G_K, and as a fixed resistor for G_L. Today, we know that the voltage-dependence of G_{Na} and G_K can be related to the biophysical properties of the individual ion channels that contribute to the macroscopic conductances. Although Hodgkin and Huxley did not know about the properties of individual membrane channels when they developed their model, it will be convenient for us to describe the voltage-dependent aspects of their model in those terms.

Gates

The macroscopic conductances of the HH model can be considered to arise from the combined effects of a large number of microscopic ion channels embedded in the membrane. Each individual ion channel can be thought of as containing one or more physical *gates* that regulate the flow of ions through the channel. An individual gate can be in one of two states, *permissive* or *non-permissive.* When *all* of the gates for a particular channel are in the permissive state, ions can pass through the channel and the channel is *open*. If any of the gates are in the non-permissive state, ions cannot flow and the channel is *closed*. Although it might seem more natural to speak of *gates* as being *open* or *closed*, a great deal of confusion can be avoided by consistently using the terminology *permissive* and *non-permissive* for gates while reserving the terms *open* and *closed* for channels.

The voltage-dependence of ionic conductances is incorporated into the HH model by assuming that the probability for an individual gate to be in the permissive or non-permissive state depends on the value of the membrane voltage. If we consider gates of a particular type *i*, we can define a probability p_i, ranging between 0 and 1, which represents the *probability* of an individual gate being in the permissive state. If we consider a large number of channels, rather than an individual channel, we can also interpret p_i as the fraction of gates in that population that

are in the permissive state. At some point in time t, let $p_i(t)$ represent the fraction of gates that are in the permissive state. Consequently 1- p_i (t) must be in the non-permissive state.

$$\begin{array}{c}\textit{fraction in} \\ \textit{non}-\textit{permissive} \\ \textit{state,}\ 1-p_i(t)\end{array} \quad \underset{b_i(V)}{\overset{a_i(V)}{\rightleftarrows}} \quad \begin{array}{c}\textit{fraction in} \\ \textit{permissive} \\ \textit{state,}\ p_i(t)\end{array}$$

The rate at which gates transition from the non-permissive state to the permissive state is denoted by a variable $a_i(V)$, which has units of sec^{-1}. Note that this "rate constant" is not really constant, but depends on membrane voltage V. Similarly there is a second rate constant, $b_i(V)$ describing the transition rate from the permissive to the non-permissive state. Transitions between permissive and non-permissive states in the HH model are assumed to obey first-order kinetics:

$$\frac{dp_i}{dt} = a_i(V)(1-p_i) - b_i(V)\,p_i \tag{4}$$

where $a_i(V)$ and $b_i(V)$ are voltage-dependent. If the membrane voltage V_m is clamped at some fixed value V, then the fraction of gates in the permissive state will eventually reach a steady state value (i.e., $dp_i/dt = 0$) as $t \to \infty$ given by:

$$p_{i,t\to\infty} = \frac{a_i(V)}{a_i(V) + b_i(V)} \tag{5}$$

The time course for approaching this equilibrium value is described by a simple exponential with time constant $t_i(V)$ given by:

$$t_i(V) = \frac{1}{a_i(V) + b_i(V)} \tag{6}$$

When an individual channel is open, it contributes some small, fixed value to the total conductance and zero otherwise. The macroscopic conductance for a large population of channels is thus proportional to the number of channels in the open state, which is in turn proportional to the probability that the associated gates are in their permissive state. Thus the macroscopic conductance G_k due to channels of type k, with constituent gates of type i, is proportional to the *product* of the individual gate probabilities p_i:

$$G_k = \bar{g}_k \prod_i p_i \tag{7}$$

where $\bar{g}_k$ is a normalization constant that determines the maximum possible conductance when all the channels are open (i.e. all gates are in the permissive state).

We have presented Eqs. 4–7 using a generalized notation that can be applied to a wide variety of conductances beyond those found in the squid axon. To conform to the standard notation of the HH model, the probability variable p_i in Eqs. 4–7 is replaced by a variable that represents the gate type. For example, Hodgkin and Huxley modeled the sodium conductance

using three gates of a type labeled "*m*" and one gate of type "*h*". Applying Eq. 7 to the sodium channel using both the generalized notation and the standard notation yields:

$$G_{Na} = \overline{g}_{Na} p_m^3 p_h = \overline{g}_{Na} m^3 h \tag{8}$$

Similarly, the potassium conductance is modeled with 4 identical "*n*" gates:

$$G_K = \overline{g}_K p_n^4 = \overline{g}_{Na} n^4 \tag{9}$$

Summarizing the ionic currents in the HH model in standard notation, we have:

$$I_{ion} = \overline{g}_{Na} m^3 h(V_m - E_{Na}) + \overline{g}_K n^4 (V_m - E_K) + g_L (V_m - E_L) \tag{10}$$

$$\frac{dm}{dt} = a_m(V)(1-m) - b_m(V)m \tag{11}$$

$$\frac{dh}{dt} = a_h(V)(1-h) - b_h(V)h \tag{12}$$

$$\frac{dn}{dt} = a_n(V)(1-n) - b_n(V)n \tag{13}$$

To completely specify the model, the one task that remains is to specify how the six rate constants in Eqs. 11–13 depend on the membrane voltage. Then Eqs. 10–13, together with Eq. 1, completely specify the behavior of the membrane potential V_m in the HH model of the squid giant axon.

Sign Conventions

Note that the appearance of I_{ion} on the left-hand side of Eq. 1 and I_{ext} on the right indicates that they have opposite *sign conventions*. As the equation is written, a positive external current I_{ext} will tend to depolarize the cell (i.e., make V_m more positive) while a positive ionic current I_{ion} will tend to hyperpolarize the cell (i.e., make V_m more negative). This sign convention for ionic currents is sometimes referred to as the neurophysiological or physiologists' convention. This convention is conveniently summarized by the phrase "inward negative", meaning that an inward flow of positive ions into the cell is considered a negative current. This convention perhaps arose from the fact that when one studies an ionic current in a voltage clamp experiment, rather than measuring the ionic current directly, one actually measures the clamp current which is necessary to counterbalance it. Thus an inward flow of positive ions is observed as a negative-going clamp current, hence explaining the "inward negative" convention. Some neural simulation software packages, such as GENESIS, use the opposite sign convention (inward positive), since that allows all currents to be treated consistently. In the figures shown in this chapter, membrane currents are plotted using the neurophysiological convention (inward negative).

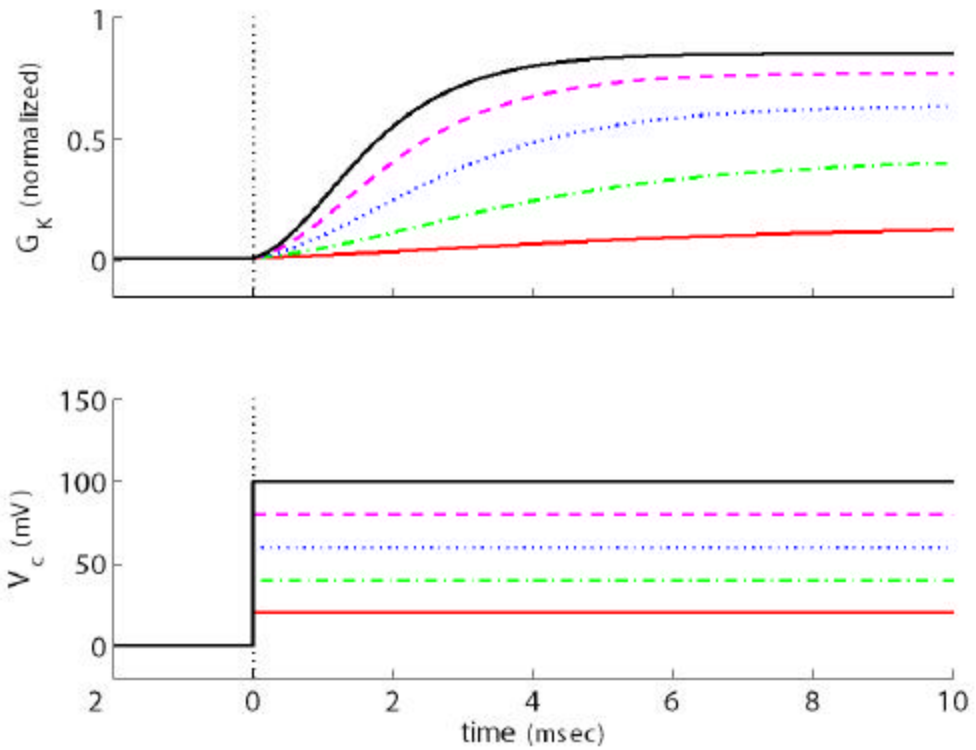

Fig. 2 Simulated voltage-clamp data illustrating voltage-dependent properties of the K^+ conductance in squid giant axon. The command voltage $V_c(mV)$ is shown in the lower panel and the K^+ current in the upper panel. Simulation parameters are from the Hodgkin and Huxley model (1952).

Voltage conventions

While we're on the topic of *conventions*, there are two more issues that should be discussed here. The first concerns the *value* of the membrane potential V_m. Recall that potentials are relative; only potential differences can be measured directly. Thus when defining the intracellular potential V_m, one is free to choose a convention that defines the resting intracellular potential to be zero (the convention used by Hodgkin and Huxley), or one could choose a convention that defines the extracellular potential to be zero, in which case the resting intracellular potential would be around −70 mV. In either case the potential *difference* across the membrane is the same, it's simply a matter of how "zero" is defined. Most simulation software packages allow the user to select a voltage reference convention they like.

The second convention we need to discuss concerns the *sign* of the membrane potential. The modern convention is that depolarization makes the membrane potential V_m more positive. However, Hodgkin and Huxley (1952) used the opposite sign convention (depolarization negative) in their paper. In the figures in this chapter, we use the modern convention that depolarization is positive.

At a conceptual level, the choice of conventions for currents and voltages is inconsequential, however at the implementation level it matters a great deal, since inconsistencies will cause the model to behave incorrectly. The most important thing in choosing conventions is to ensure that the choices are internally consistent. One must pay careful attention

to these issues when implementing a simulation using equations from a published model, since it may be necessary to convert the empirical results reported using one set of conventions into a form that is consistent with one's own model conventions.

Rate Constants

How did Hodgkin and Huxley go about determining the voltage-dependence of the rate constants a and b that appear in equations Eqs. 11–13? How did they determine that the potassium conductance should be modeled with four n gates, but that the sodium conductance required three m gates and one h gate? In order to answer these questions, we need to look in more detail at the type of data that can be obtained from voltage-clamp experiments.

Fig. 2 shows simulated voltage-clamp data, similar to those obtained by Hodgkin and Huxley in their studies of squid giant axon. In these experiments, Hodgkin and Huxley used voltage clamp circuitry to step the membrane potential from the resting level (0 mV) to a steady depolarized level. The figure shows the time course of the change in normalized K^+ conductance for several different voltage steps. Three qualitative effects are apparent in the data. First, the steady-state conductance level increases with increasing membrane depolarization. Second, the onset of the conductance change becomes faster with increasing depolarization. Third, there is a slight temporal delay between the start of the voltage step and the change in conductance.
In the simulated voltage clamp experiments illustrated in Fig. 2, the membrane potential starts in the resting state (V_m = 0, using the HH voltage convention) and is then instantaneously stepped to a new clamp voltage V_c. What is the time course of the state variable n, that controls gating of the K^+ channel, under these circumstances? Recall that the differential equation governing the state variable n is given by:

$$\frac{dn}{dt} = a_n(V)(1-n) - b_n(V)n \tag{14}$$

Initially, with V_m = 0, the state variable n has a steady-state value (i.e., when dn/dt = 0) given by Eq. 5:

$$n_\infty(0) = \frac{a_n(0)}{a_n(0) + b_n(0)} \tag{15}$$

When V_m is clamped to a new level V_c, the gating variable n will eventually reach a new steady-state value given by:

$$n_\infty(V_c) = \frac{a_n(V_c)}{a_n(V_c) + b_n(V_c)} \tag{16}$$

The solution to Eq. 14 that satisfies these boundary conditions is a simple exponential of the form:

$$n(t) = n_\infty(V_c) - (n_\infty(V_c) - n_0(0))e^{-t/t_n(V_c)} \tag{17}$$

Given Eq. 17, which describes the time course of n in response to a step change in command voltage, one could try fitting curves of this form to the conductance data shown in Fig.

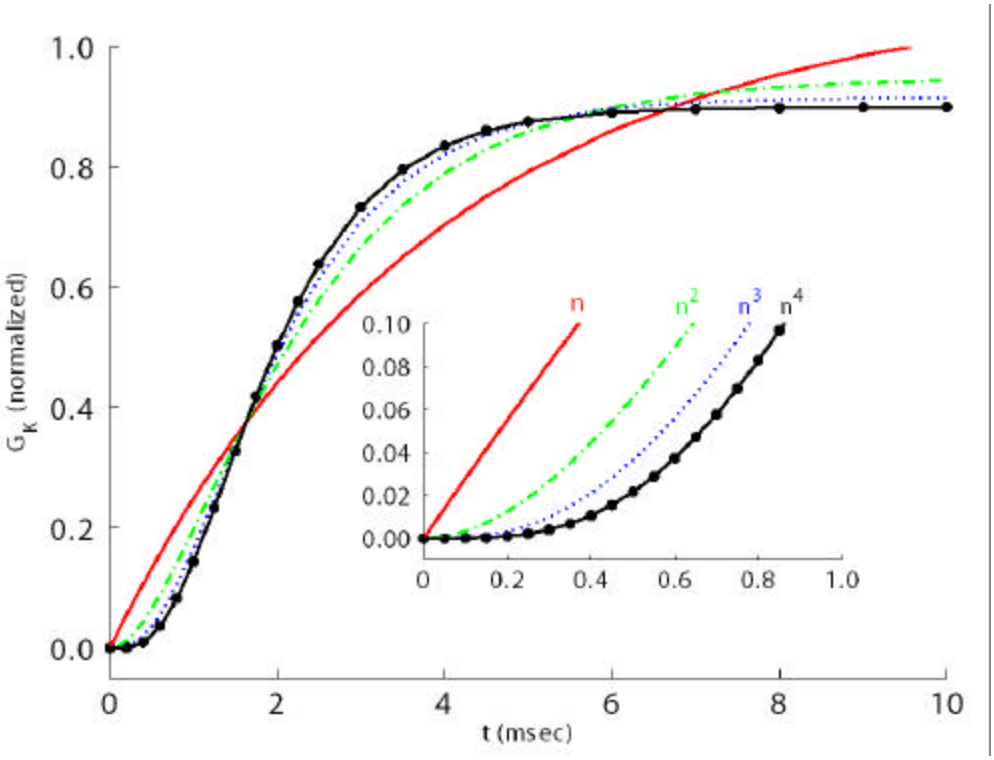

Fig. 3 Best fit curves of the form $G_k = \bar{g}_K n^j$ (*j* = 1–4) for simulated conductance vs. time data. The inset shows an enlargement of the first millisecond of the response. The initial inflection in the curve cannot be well-fit by a simple exponential (dotted line) which rises linearly from zero. Successively higher powers of *j* (*j*=2: dot-dashed; *j*=3: dashed line) result in a better fit to the initial inflection. In this case, *j*=4 (solid line) gives the best fit.

2 by finding values of $n_\infty(V_c)$, $n_\infty(0)$, and $t_n(V_c)$ that give the best fit to the data for each value of V_c. Fig. 3 illustrates this process, using some simulated conductance data generated by the Hodgkin-Huxley model. Recall that *n* takes on values between 0 and 1, so in order to fit the conductance data, *n* must be multiplied by a normalization constant $\bar{g}_K$ that has units of conductance. For simplicity, the normalized conductance $G_K / \bar{g}_K$ is plotted. The dotted line in Fig. 3 shows the best-fit results for a simple exponential curve of the form given in Eq. 17. While this simple form does a reasonable job of capturing the general time course of the conductance change, it fails to reproduce the sigmoidal shape and the temporal delay in onset. This discrepancy is most apparent near the onset of the conductance change, shown in the inset of Fig. 3. Hodgkin and Huxley realized that a better fit could be obtained if they considered the conductance to be proportional to a higher power of *n*. Figure 3 shows the results of fitting the conductance data using a form $G_K = \bar{g}_k n^j$ with powers of *j* ranging from 1 to 4. Using this sort of fitting procedure, Hodgkin and Huxley determined that a reasonable fit to the K^+ conductance data could be obtained using an exponent of *j=4*. Thus they arrived at a description for the K^+ conductance under voltage clamp conditions given by:

$$G_K = \bar{g}_K n^4 = \bar{g}_K \left[n_\infty(V_c) - (n_\infty(V_c) - n_\infty(0)) e^{-t/t_n} \right]^4 \qquad (18)$$

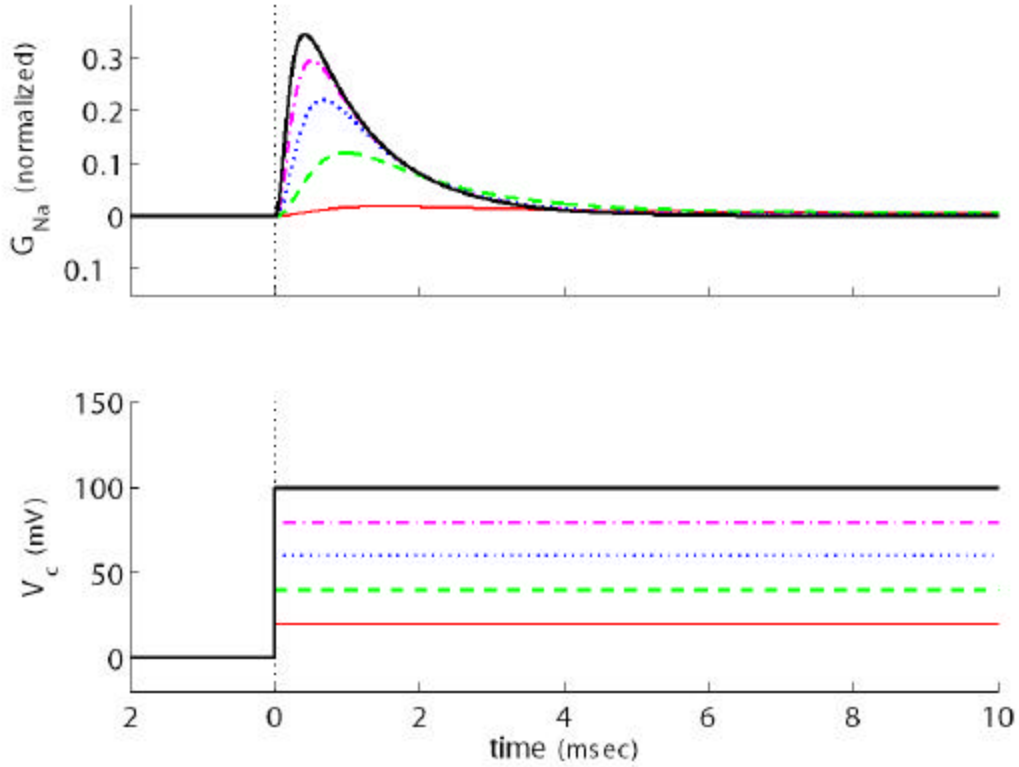

Fig. 4 Simulated voltage-clamp data illustrating activation and inactivation properties of the Na^+ conductance in squid giant axon. The command voltage V_c is shown in the lower panel and the Na^+ current in the upper panel. Simulation parameters are from the Hodgkin and Huxley model (1952).

Activation and Inactivation gates

The strategy Hodgkin and Huxley used for modeling the sodium conductance is similar to that described above for the potassium conductance, except that the sodium conductance shows a more complex behavior. In response to a step change in clamp voltage, the sodium conductance exhibits a transient response (Fig. 4), whereas the potassium conductance exhibits a sustained response (Fig. 2). Sodium channels inactivate whereas the potassium channels do not. To model this process, Hodgkin and Huxley postulated that the sodium channels had two types of gates, an activation gate, which they labeled *m*, and an inactivation gate, which they labeled *h*. Again, boundary conditions dictated that *m* and *h* must follow a time course given by:

$$m(t) = m_\infty(V_c) - (m_\infty(V_c) - m_\infty(0))e^{-t/t_m(V_c)} \tag{19}$$

$$h(t) = h_\infty(V_c) - (h_\infty(V_c) - h_\infty(0))e^{-t/t_h(V_c)} \tag{20}$$

Hodgkin and Huxley made some further simplifications by observing that the sodium conductance in the resting state is small compared to the value obtained during a large depolarization, hence they were able to neglect $m_\infty(0)$ in their fitting procedure. Likewise, steady state inactivation is nearly complete for large depolarizations, so $h_\infty(V_c)$ could also be eliminated

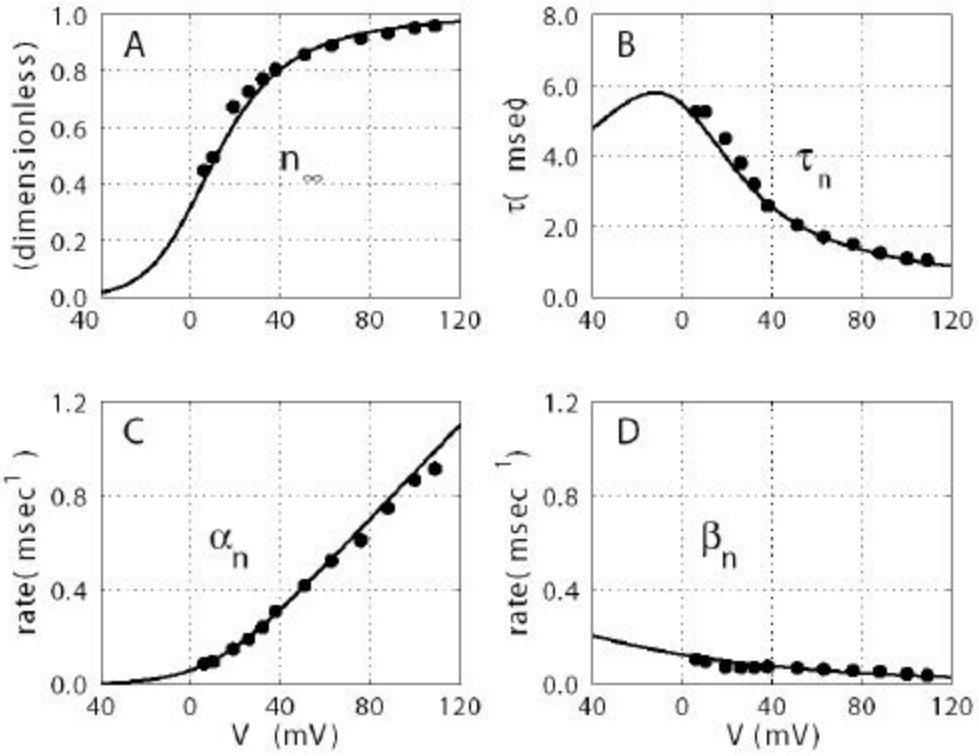

Fig. 5 Parametric fits to voltage-dependence of the K^+ conductance in the HH model. (A) Steady-state value n_∞; (B) time constant t_n (C) forward rate constant a_n; and (D) backward rate constant b_n. Data points are from Table 1 of Hodgkin and Huxley (1952). Solid lines in (C) and (D) are parametric fits to the rate data. The best fit curves correspond to Eqs. 23 and 24, respectively. Solid lines in (A) and (B) are the transformations of the a/b **functions into the n_∞ / t representation using Eqs. 5 and 6.**

from the fitting procedure. With these simplifications, Hodgkin and Huxley were able to fit the remaining parameters from the voltage clamp data. The sodium conductance G_{Na} was thus modeled by an expression of the form $G_{Na} = \overline{g}_{Na} m^3 h$.

Parameterizing the rate constants

By fitting voltage clamp data as discussed above, steady-state conductance values and time constants can be empirically determined as a function of command voltage for each of the gating variables associated with a particular channel. Using Eqs. 5 and 6, the steady-state conductance values and time constants can be transformed into expressions for the forward and backward rate constants a and b. For example, for the potassium channel *n* gate:

$$a_n(V) = \frac{n_\infty(V)}{t_n(V)} \tag{21}$$

$$b_n(V) = \frac{1 - n_\infty(V)}{t_n(V)} \tag{22}$$

Thus there are two equivalent representations for the voltage dependence of a channel. One representation specifies the voltage dependence of the rate constants, which we'll call the a / b representation. The other representation specifies the voltage dependence of the steady state conductance and the time constant, which we'll call the n_∞ / t representation. These two representations are interchangeable and one can easily convert between them using the algebraic relationships in Eqs. 5 and 6 (for transforming from a / b to n_∞ / t) and Eqs. 21 and 22 (for transforming from n_∞ / t to a / b). In general, experimentalists tend to use the n_∞ / t representation because it maps more directly onto the results of voltage-clamp experiments. Modelers, on the other hand, tend to express voltage-dependencies using the a / b representation, because it maps more directly onto the gating equations (Eqs. 11-13) in the standard formulation of the Hodgkin-Huxley model.

Voltage clamp experiments yield estimates of n_∞ / t or a / b only at the discrete clamp voltages V_c used in the experiment. Numerical integration of the HH model, however, requires that n_∞ / t or a / b values be specified over a continuous range of membrane voltages, since the membrane potential varies continuously in the model. Typically, voltage dependencies are expressed as a continuous function of voltage, and the task for the modeler becomes one of determining the parameter values that best fit the data. As an illustration, the closed circles in Fig. 5Arepresent B empirical data on $n_\infty(V_c)$ and $t_n(V_c)$ obtained by Hodgkin and Huxley (Table 1, Hodgkin and Huxley, 1952). The data points in Fig. 5CD show the same data set transformed into the a / b representation. Hodgkin and Huxley used the following functional forms to parameterize their K^+ conductance results (shown as solid lines in Fig. 5):

$$a_n(V) = \frac{0.01(10 - V)}{\exp(\frac{10 - V}{10}) - 1} \tag{23}$$

$$b_n(V) = 0.125 \exp(-V / 80) \tag{24}$$

If Eqs. 23 and 24 above are compared with Eqs. 12 and 13 from the original paper (Hodgkin and Huxley, 1952), you will note that the sign of the membrane voltage has been changed to correspond to the modern convention (see subsection on Voltage Conventions above). Hodgkin and Huxley used similar functional forms to describe the voltage dependence of the *m* and *h* gates of the sodium channel:

$$a_m(V) = \frac{0.1(25 - V)}{\exp(\frac{25 - V}{10}) - 1} \tag{25}$$

$$b_m(V) = 4 \exp(-V / 18) \tag{26}$$

$$a_h(V) = 0.07 \exp(-V / 20) \tag{27}$$

$$b_h(V) = \frac{1}{\exp(\frac{30 - V}{10}) + 1} \tag{28}$$

In neural simulation software packages, the rate constants in HH-style models are often parameterized using a generic functional form:

$$a(V) = \frac{A + BV}{C + H\exp(\frac{V + D}{F})} \tag{29}$$

In general, this functional form may require up to six parameters (*A, B, C, D, F, H*) to fully specify the rate equation. However, in many cases adequate fits to the data can be obtained using far fewer parameters. Fortunately, Eq. 29 is flexible enough that it can be transformed into simpler functional forms by setting certain parameters to either 0 or 1. For example, if the voltage clamp data can be adequately fit by an exponential function over the relevant range of voltages, then setting *B*=0, *C*=0, *D*=0 and *H*=1 in Eq. 29, results in a simple exponential form, $a(V) = A\exp(-V/F)$, with just two free parameters (*A* and *F*) to be fit to the data. Similarly, setting *B*=0, *C*=1 and *H*=1 gives a sigmoidal function with three free parameters (*A*, *D*, and *F*).

One other technical note is that certain function forms can become indeterminate at certain voltage values. For example, the expression for $a_n(V)$ in Eq. 23 evaluates to the indeterminate form *0/0* at *V=10*. The solution to this problem is to apply L'Hospital's rule, which states that if *f*(*x*) and *g*(*x*) approach *0* as *x* approaches *a*, and $f'(x)/g'(x)$ approaches *L* as *x* approaches *a*, then the ratio $f(x)/g(x)$ approaches *L* as well. Using this rule, it can be shown that $a_n(10) = 0.1$. When implementing HH-style rate functions in computer code, care must be taken to handle such cases appropriately.

Reference

Hodgkin AL, Huxley AF (1952) A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol. (London)* 117, 500-544.